Surgical insights into Parkinson's disease

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SUMMARY

Surgery for Parkinson's disease was popularized in the mid-twentieth century before the advent of effective medical therapies. Early lesioning treatments contributed to our understanding of the functional anatomy of Parkinson's disease. Observations of the limitations and long-term complications of established pharmacological therapies for Parkinson's disease, together with major contributions from animal research to elucidate the roles of the basal ganglia in movement disorders, inspired a recent renaissance in neurosurgical interventions for Parkinson's disease including deep brain stimulation; this continues to yield much neurophysiological information. The development of potentially restorative treatment modalities, such as gene therapy, neural transplantation and nanotechnology, hold much promise for surgery, both therapeutically and in revealing further insights into Parkinson's disease pathophysiology.

INTRODUCTION

Parkinson's disease is a slowly progressive, neurodegenerative disease characterized by tremor, rigidity, bradykinesia and postural instability. It is the most common movement disorder in middle or late life with a prevalence of about 0.3% of the general population, rising to 1% in people over 60 years of age.¹ Approximately 130 000 people suffer from it in the UK and it presents an increasing burden in our ageing population. Pathological findings in Parkinson's disease demonstrate greatly diminished neuromelanin pigmented neurons in the substantia nigra of the basal ganglia with associated gliosis, and Lewy bodies present in many remaining neurons. Its cardinal biochemical feature is dopamine deficiency in the striatum, another basal ganglia structure. The brain structures currently targeted in surgery for Parkinson's disease are predominantly in the basal ganglia and include the globus pallidus interna, ventralis intermedius nucleus of the thalamus, and subthalamic nucleus (Figure 1).

James Parkinson, in his original 1817 *Essay on The Shaking Palsy*, gave an account of six patients in which he noted signs of tremor, festinating gait and flexed posture.²

He commented in the monograph that '... until we are better informed respecting the nature of this disease the employment of internal medicines is scarcely warrantable'. Nearly two centuries on from Parkinson's observations, and almost four decades after Cotzias' dramatic demonstration of levodopa's efficacy,³ the limitations and complications of levodopa treatment for Parkinson's disease have become well documented (Table 1).⁴ The now established resurgence of neurosurgery for Parkinson's disease, in particular of deep brain stimulation (DBS) for the treatment

Figure 1 A coronal section through a cerebral hemisphere illustrating the basal ganglia. STR, striatum; GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; Th, thalamus; subthalamic nucleus; STN, subthalamic nucleus; SNr, substantia nigra pars reticulata; SNc, substantia nigra pars compacta [in colour online]

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Table 1 Motor complications of long-term levodopa treatment

<i>Hypokinetic phenomena</i>	<i>Hyperkinetic phenomena</i>
End of dose 'wearing off' bradykinesia	Peak dose dyskinesia
Unpredictable 'on/off' bradykinesia	Diphasic dyskinesia
Brief 'off' period freezing	'Off' period dyskinesia
Brief 'on' period freezing	Early morning dystonia
Early morning akinesia or bradykinesia	Biphasic dystonia

of tremor and dyskinesias refractory to medication, encourages reflection upon the insights gained from surgery into the pathophysiology of the disease. Here, we consider whether surgery has informed us sufficiently to warrant 'the employment of internal medicines' and evaluate the future prospects for surgical intervention in Parkinson's.

METHODS

References were identified from the authors' reading of books and journals in neuroscience, neurology and neurosurgery; from electronic literature (Medline) searches; and through discussions with colleagues. Because of the broad nature of topics covered, accessible reviews have sometimes been cited rather than primary data papers.

ABLATION AS THERAPY

The counter-intuitive, albeit now vindicated, strategy of employing surgical ablation to improve an already impaired nervous system has its origins with Parkinson himself. He noted that the resting tremor of one of his patients disappeared with a stroke that rendered them hemiplegic.² However, he speculated that the disease arose from medullary swelling impeding the passage of nervous influence from brain to muscle; the basal ganglia were not implicated in movement disorders until Hughlings Jackson's observations half a century after Parkinson's original description.⁵ Their role was not popularized until another half a century later again when Ramsey Hunt proposed that lesions to different components of the basal ganglia could cause parkinsonism, chorea and athetosis.⁶ His theory built upon foundations laid by Wilson in primate brain lesioning experiments using Horsley and Clarke's recently invented stereotactic apparatus.^{7,8} The 'inhibition release' hypotheses of Hughlings Jackson, Ramsey Hunt, Wilson and others prevailed until the 1980s; despite their inability to account for many clinical sequelae of movement disorders, for example the great variety of motor manifestations of Huntington's disease. Wilson coined the basal ganglia 'dark basements of the mind' and they remained a mystery.⁹ Nevertheless, the hypotheses and experimental evidence available were sufficient to

encourage a host of attempts at surgical lesioning for the treatment of Parkinson's throughout the first half of the twentieth century.

Many surgeons targeted the basal ganglia, yet targets varied dramatically in brain and spine, notably including Bucy's pioneering motor cortex extirpations.¹⁰ Most operations conferred little clinical benefit, and even included thyroidectomy.^{11,12} As Laitinen remarked,

'When one sets out to make a historical survey of surgical attempts to relieve the tremor and rigor in Parkinson's disease, one cannot help feeling that it would have been a far easier task to list those nervous structures which have not been attacked'.¹³

Nevertheless, the poor results obtained by the disparate multitude of freehand surgical approaches helped, at the very least, to clarify many anatomical structures neither necessary to nor sufficient for Parkinson's.

In 1952, the American neurosurgeon Cooper operated upon a patient with the disease and inadvertently ligated their anterior choroidal artery causing infarction of the globus pallidus. His patient awoke with their tremor resolved and no deficits despite the damage done.¹⁴ Cooper's finding led to the relatively effective practice of injecting alcohol into the globus pallidus to relieve Parkinsonian tremor. The creation in 1947 of a stereotactic frame for localizing surgical targets using human brain rather than skull landmarks gave new opportunities for accurate ablation of brain structures.¹⁵ In the same decade as Cooper's discovery, Leksell utilized his own recently invented stereotactic apparatus to accurately lesion the posteroventrolateral portion of the globus pallidus interna by thermocoagulation to ameliorate parkinsonian bradykinesia and rigidity in over 200 patients.¹⁶⁻¹⁸ Thalamic ablation was also introduced in the early 1950s; it was found to relieve tremor and rigidity with little improvement in hypokinesia but more consistent benefits than medial, if not posteroventrolateral, pallidotomy.¹⁹ Thus, thalamotomy became the most common surgical intervention for Parkinson's disease with over 70 000 patients having been operated upon by the mid 1970s, waning only as levodopa established itself as the mainstay of the

treatment. However, the risks of ablative surgery can be significant,^{20,21}—they include:

- haemorrhage
- infarction
- facial palsies
- dysphagia
- visual field, speech and cognitive deficits
- affective disorders
- mortality

Furthermore, despite the empirical clinical benefit shown by such operations, they revealed little mechanistically regarding the dysfunctional circuitry underlying Parkinson's disease.

ANIMAL RESEARCH

The absence of a plausible theoretical model, juxtaposed against the clinical improvements shown during two decades of surgery and the dramatic benefits conferred by the recently discovered drug levodopa, prompted Marsden, a renowned authority on movement disorders, in 1975 to assert that

*'much of the research into experimental parkinsonism and dyskinesias must be undertaken in primates, for only those animals develop the typical clinical phenomena seen in man'.*²²

Animal research up until then had contributed considerably towards understanding the pathophysiology and treatment of Parkinson's disease. There were notable works which included: Hughlings Jackson's primate research leading to his conclusion that unstable basal ganglia activity led to chorea;⁵ Sherrington's development of the decerebrate animal as a model of parkinsonian rigidity;²³ Fulton's demonstrations that cerebellar tremor could be relieved by motor cortex lesions;²⁴ Denny-Brown's many primate lesioning experiments leading to his postulate that movement disorders arise from conflicts between postural reflexes due to basal ganglia dysfunction;²⁵ and Carlsson's demonstration that levodopa reversed akinesia in reserpinized animals.²⁶ However, as Marsden predicted, it was the development of increasingly accurate primate models of the disease that enabled great advances in the theoretical understanding to be made.

In 1983 several cases of parkinsonism in heroin users led to the discovery that the compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces parkinsonism in humans.²⁷ Thus, a primate model of parkinsonism was created which remains the only mammalian model to exhibit the resting tremors and drug-induced dyskinesias seen in humans.²⁸ Evidence gathered from several years' worth of metabolic marker studies,²⁹ and recordings of

single neuron activities in awake, moving primates enabled the conception of a theory for basal ganglia function that could finally explain the symptoms and signs of Parkinson's disease.^{30,31} The experiments of DeLong, Crossman and others led to a proposal that neural circuitry comprising 'direct' and 'indirect' pathways is dysfunctional in the disease (Figure 2), and also that parallel circuits linking neocortical brain structures with the basal ganglia are involved in cognitive and emotional processing. Dysfunction within such a parallel 'cortico-striato-pallido-thalamic' neuronal network explained not only motor phenomena, but provided a plausible paradigm to explain many of the cognitive, affective and behavioural changes seen in Parkinson's disease and other movement disorders and, conversely, the motor changes seen in psychiatric disorders.³²⁻³⁴ In the early 1990s, it was demonstrated that lesions made to the subthalamic nucleus in primates reversed the motor symptoms of MPTP-induced parkinsonism.^{35,36} Together with the resurgence of globus pallidus interna ablation pioneered in Sweden in the late 1980s for Parkinson's disease refractory to levodopa treatment,³⁷ this finding and the development of DBS led to a veritable renaissance in surgical treatment for the disease.

The MPTP primate model is the most useful animal model of Parkinson's disease available presently. Primates are bipedal species whose nervous systems emulate the size and complexity of the human nervous system; and they are dexterous enough to perform the delicate motor tasks required to evaluate their motor function experimentally. The MPTP primate is not a perfect model and its utility and limitations have been comprehensively reviewed.³⁸⁻⁴¹ Despite its successful mimicry of parkinsonian symptoms, one particular shortcoming is its inability to replicate the insidious onset and progressive degeneration of Parkinson's disease. Nevertheless, it is accurate enough to have proven invaluable to the preclinical investigation of both surgical and pharmacological treatments.^{42,43}

DEEP BRAIN STIMULATION

Reversible lesioning by DBS was pioneered by Cooper for treating spasticity and epilepsy in the early 1970s,⁴⁴ but was not applied to Parkinson's disease until 1987 when DBS, using indwelling electrodes inserted into the thalamus, was shown to suppress tremor.⁴⁵ Bilateral DBS of either the globus pallidus interna or the subthalamic nucleus dramatically improves parkinsonian tremor, bradykinesia and rigidity (Figure 3).^{46,47} Approximately 30 000 patients worldwide have benefited from DBS to date. However, the procedure remains limited to specialist centres, and appropriate patient selection is crucial to its successful use (Box 1).⁴⁸ Few randomized clinical trials comparing DBS to pharmacological treatments have been done,⁴⁹ although a

Figure 2 Basal ganglia circuitry involved in movement. GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; STN, subthalamic nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; VL, ventrolateral thalamus; PPN, pedunculopontine nucleus [in colour online]

large multi-centre prospective clinical trial is currently underway in the UK.⁵⁰

Globus pallidus interna DBS may directly reduce medication induced dyskinesias but subthalamic nucleus DBS may achieve the same goal by enabling patients to reduce their levodopa dosage radically. While the subthalamic nucleus has recently gained wider acceptance as a surgical target, further large, prospective clinical trials are required to confirm its long-term superiority.⁵¹ The present impression is that globus pallidus interna DBS may be a superior treatment for patients with a low dyskinesia threshold and low levodopa dosage but that subthalamic nucleus DBS may be better for those using large amounts of levodopa. Also under investigation are the effects of DBS upon non-motor sequelae of Parkinson's disease: cognitive; affective and behavioural;⁵² upon quality of life;⁵³ and upon the natural history of the disease. It has been speculated that subthalamic nucleus DBS is neuroprotective, inhibiting glutamatergic afferent-mediated excitotoxic damage to dopaminergic nigrostriatal neurons and thus slowing disease progression.⁵⁴ However, evidence is equivocal and further research is needed.⁵⁵

Current anatomical models of basal ganglia function (Figure 2) fail to explain wholly the efficacy of DBS in Parkinson's disease: in particular the finding that globus pallidus interna DBS paradoxically improves dyskinesias without deleterious effects upon motor function.^{56,57} One

hypothesis implicates aberrantly modulated rhythmic activity in different basal ganglia neurons oscillating in synchrony at different frequency bands to account for both the pathological movements of Parkinson's disease and the efficacy of surgical lesions and DBS.⁵⁸ Further research is needed, both experimentally and from electrode recordings in patients, to gain a fuller understanding of such mechanisms. Animal research also continues to reveal

Box 1 Selection criteria for surgery in Parkinson's disease

- Idiopathic Parkinson's disease
- Dopamine responsive symptoms
- Patient desire for consistent reduction of increased duration in motor symptoms
- Minimal cognitive impairment (MMSE > 24/30)
- Depression or mood disorders minimal or well controlled by medication
- No psychotic symptoms or hallucinations induced by medications
- Good bulbar neurological function

MMSE, mini-mental state examination

Figure 3 Electrode implantation for deep brain stimulation in Parkinson's disease [in colour online]

new roles in the disease for brain structures related to the basal ganglia, such as the pedunculo-pontine nucleus.⁵⁹ These findings provide exciting possibilities for novel therapeutic targets for DBS that are already beginning to reach the clinic.^{60,61}

RESTORATIVE SURGERY—QUO VADIS?

Potential cellular and molecular therapies for the disease include gene therapy, neural tissue transplantation and nanotechnology. Of these, both neural transplantation and gene therapy have reached clinical trials.

Neural transplantation aims to replace the nigrostriatal neurons that release the neurotransmitter dopamine and then degenerate in this disease. The many donor cell sources under consideration include porcine neural xenografts, human fetal tissue and human stem cells. For fetal tissue, anatomical and functional imaging studies have supported clinical evidence of graft survival and functionality.⁶² However, clinical trials have resulted in complications of dyskinesia after transplantation.^{63,64} Such

dyskinesias are hypothesized to arise from altered dopamine release, but the mechanisms remain contentious and some have suggested that they may only occur in certain subgroups of patients.⁶⁵ The trials performed have been upon small numbers of patients with little consistency in graft amounts and grafting techniques used. Furthermore, the technique may be limited by ethical concerns and limited donor sources.

One promising form of gene therapy that may soon reach clinical trials involves introducing enzymes required for dopamine synthesis into the striatum. Good results have been demonstrated in restoring motor function in a rodent model of parkinsonism.⁶⁶ Other gene therapies currently being trialled in patients aim to:

- replace neurotransmitters like gamma-aminobutyric acid (GABA) to alter basal ganglia neuronal circuitry functions
- or to insert neural growth factors like glial cell-line derived neurotrophic factor (GDNF) to arrest or reverse the degeneration of nigrostriatal neurons.

Viral vectors are considered more likely to be efficient, practical and safe than constant infusions of recombinant factors for the delivery of gene therapy at present, and may also confer the advantage of requiring a single treatment only. Furthermore, it is suggested that neurotrophic gene therapy is, in principle, less likely to cause unwanted dyskinesias: it aims to restore pre-existing neural function, rather than replace it as neural transplantation aims to do. Further research is required to confirm both that gene therapy is safe and that its functional restoration is lasting.

Looking to the future beyond neural transplantation and gene therapy, molecular nanotechnology is the three-dimensional control of atoms and molecules to produce materials with novel properties. Alongside advances in biological imaging that such technologies will enable, nanomaterials like nanotubes could be used therapeutically as ligand carriers or vectors for drug or gene delivery.^{67,68} Nanomanufacturing aims to produce functional biological macromolecules that can operate *in vivo* while being controlled *ex vivo*; one possibility would be the manufacture of dopamine producing nigrostriatal neurons whose level of activity could be modulated exogenously as required. The technology remains experimental and far from clinical trials at present, but nanosurgery holds great promise for the future of surgery in Parkinson's disease.

Amidst all the excitement surrounding cellular and molecular treatments for Parkinson's disease, it should be noted that merely attempting to restore dopamine release from nigrostriatal neurons may remain limited in the extent to which it addresses the problems. Thus, shifts of research focus may be preferable: first, towards halting disease

progression; and, secondly, towards understanding its aetiology with a view to disease prevention.⁶⁹ As the best models of Parkinson's disease are currently primate models, they will continue to be vital, both to characterizing the onset and progression of parkinsonian degeneration, and in the development of preventative strategies.

CONCLUSIONS

Much has been learnt about Parkinson's disease from surgical interventions. The ablative procedures undertaken before the era of levodopa helped delineate anatomical structures implicated in the disease. Alongside serendipitous clinical discoveries, empirical observations in patients and technological advances, valuable progress has been made because of controlled experiments enabled by the availability of an accurate animal model. The example of DBS of the subthalamic nucleus demonstrates a therapy whereby primate research has not only been essential to advancing our theoretical framework, but also provided evidence to justify clinical trials in patients leading to successful treatment.

The surgical treatment of DBS provides amelioration of Parkinson's disease motor symptoms and relief from motor complications of medical treatment. Measurements made from indwelling electrodes in patients continue to give new insights into the functional anatomy and pathophysiology of the disease. Other targeted surgical therapies like gene therapy, neural transplantation and nanotechnology show much promise; but they require robust demonstration of their safety and efficacy in animal models before progressing to clinical trials. Novel surgical techniques have played—and continue to play—a crucial role in deepening our understanding of the parkinsonian brain. Their implementation requires carefully controlled clinical trials with appropriate patient selection, blinding and randomization. There are many unanswered issues relating to both motor and non-motor manifestations of Parkinson's disease and the renaissance in surgery gives much hope in that we may begin to address them.

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